prostate cancer for every 100 ng/ml increase in IGF-I levels, does not reasonably provide enablement for the full scope of the claimed methods, wherein any concentration above a reference level is deemed to indicate an increased risk for prostate cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant respectfully traverses this rejection.

The Examiner states that the specification demonstrates a linear relationship between increased IGF-I levels and risk of prostate cancer. IGF-I levels were measured in blood samples of men before and after a diagnosis of prostate cancer, and compared to IGF-I levels in matched controls, men who never developed prostate cancer. A statistical analysis demonstrated that there was a higher incidence of prostate cancer in quartiles with higher IGF-I levels, when using the lowest quartile 1 as the reference levels. However, the Examiner states that there is some question in the art as to the appropriate method to determine a reference level for IGF-I, whether to use the first quartile or a combination of the first two quartiles as the reference levels for prostate cancer prognosis, according to Wolk (Wolk, Journal of the National Cancer Institute, 90(12): 911-915, 1998) and Lash (Lash, Journal of the National Cancer Institute, 90(23): 1841, 1998). Also, there is uncertainty in the art as to whether IGF-I measurement is a useful marker for prostate cancer prognosis; the Examiner states that Cohen (Cohen, Journal of the National Cancer Institute, 90(12): 876-879, 1998) and Finne (Finne, Journal of Clinical Endocrinology & Metabolism, 85(8): 2744-2747, 2000) show that 3 of 6 studies show either no significance between IGF-I levels of prostate cancer patients and control subjects, or a decrease of IGF-I levels with prostate cancer. Further, the demonstration of

a linear trend does not indicate whether there is a significant difference between quartile 1 and quartile 2. Accordingly, one skilled in the art would need to engage in more than routine experimentation to determine a reference level, or to determine the level of change above a reference level that correlates with any amount of risk of prostate cancer. Because of the uncertainty in the art, and because the claims are broadly drawn to methods to determine a reference level and include any amount of difference above this reference level, the breadth of the claims do not appear to be commensurate with the scope of the claims.

Applicant respectfully traverses the Examiner's rejection. The specification teaches that there is a continuous linear relationship between having an IGF-I level above the reference level and risk of future development of prostate cancer (see Table 2, page 9, lines 22-24 and page 11, lines 6-11). Elevated levels of IGF-I were significantly associated with prostate cancer risk in a univariate analysis (see page 11, lines 1-5). The linear trend was such that after adjusting for IGFBP-3, a 100 ng/ml increase in IGF-I corresponded to an approximate doubling of relative risk when compared to the reference level (see page 11, lines 6-11 and Table 2). The doubling of risk for a 100 ng/ml elevation of IGF-I is described as a particular point in the linear trend. Elevations of IGF-I below 100 ng/ml would also correspond to a significantly increased risk for prostate cancer, being part of the same constant relationship over all of the measured IGF-I levels. The relationship between IGF-I levels and risk of prostate cancer development is general, rather than being confined to a particular range of IGF-I levels.

The references cited by the Examiner as describing uncertainty in the art as to the appropriate method to determine a reference level (Wolk and Lash), and also as to the

usefulness of IGF-I as a marker of prostate cancer prognosis (Cohen and Finne), describe IGF-I measurements in patients having been already diagnosed with prostate cancer. In these references, IGF-I levels are being related to cases of existing prostate cancer, rather than the risk of future development of prostate cancer in healthy individuals without prostate cancer. Therefore, any uncertainty in the art as to the use of IGF-I as a marker for prostate cancer prognosis does not indicate an uncertainty in the art as to the measurement of IGF-I in healthy individuals without prostate cancer, in order to determine the risk of future development of prostate cancer.

Because the specification demonstrates a significant linear relationship between the risk of prostate cancer and IGF-I levels that are above the reference range in healthy individuals without prostate cancer, Applicant respectfully submits that one skilled in the art would not be required to engage in undue experimentation to practice the invention as claimed. Accordingly, Applicant respectfully requests that the rejection under 35 USC 112, first paragraph, be withdrawn.

The 35 U.S.C. §102(b) rejections

Claims 21-27 remain rejected under 35 USC 102(a) as being anticipated by Mantzouros (Mantzouros *et al., British Journal of Cancer* 76(9): 1115-1118, 1997). Applicant respectfully traverses the rejection.

The Examiner states that Mantzouros teaches a method of predicting risk of prostate cancer where concentrations of IGF-I are measured in healthy individuals and where IGF-I concentrations are measured in test individuals that have either prostate cancer or BPH, and where a risk of prostate cancer is determined by comparing IGF-I

levels to a reference. Mantzouros teaches that an increase in IGF-I in 60 ng/ml leads to a 91 percent increase in risk of prostate cancer. Mantzouros performs the steps of the claimed methods and teaches a statistic to interpret a blood test results; therefore, Mantzouros teaches methods that are the same as those claimed.

Applicant respectfully traverses the Examiner's rejection. The specification describes a prospective study in which all individuals were healthy at the time sample collection; all assays reported are from blood specimens collected an average of seven years prior to clinical diagnosis of prostate cancer (see page 8, lines 16-17). In contrast, the Mantzouros study was retrospective in that blood samples were collected from individuals with histologically confirmed cases of prostate cancer or BPH, and from healthy individuals (see Abstract). Mantzouros therefore determines that levels of IGF-I are elevated in prostate cancer or BPH cases relative to healthy individuals. Mantzouros cannot determine the risk of future development of prostate cancer in a healthy individual without prostate cancer, because the elevated IGF-I levels were measured in individuals already having prostate cancer or BPH. In addition, unlike the teachings of the present specification, because of its retrospective nature the Mantzouros study could not rule out possible effects of the cancer itself, or cancer treatment, on IGF-I levels (see the paragraph spanning pages 14-15).

Applicant respectfully contends that because the methods in the present claims are not the same as those taught in Mantzouros, the present claims are not anticipated by Mantzouros. Accordingly, Applicant respectfully requests that the rejection under 35 USC 102(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed July 7, 2005. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: 12-7-05

Diagnostic Systems Laboratories, Inc.
445 Medical Center Boulevard
Webster, TX 77598
(281) 332-9678
hsoehnge@dslabs.com

Holly O. Soehnge, Ph.D., J.D.
Registration No. 54,786
Counsel for Applicant